

Process Chemistry

The Challenging Synthesis of Hydrocortisone

Role of Medicinal Chemist vs. Process Chemist

Medicinal chemists role:

Identify the chemical that will make a good drug

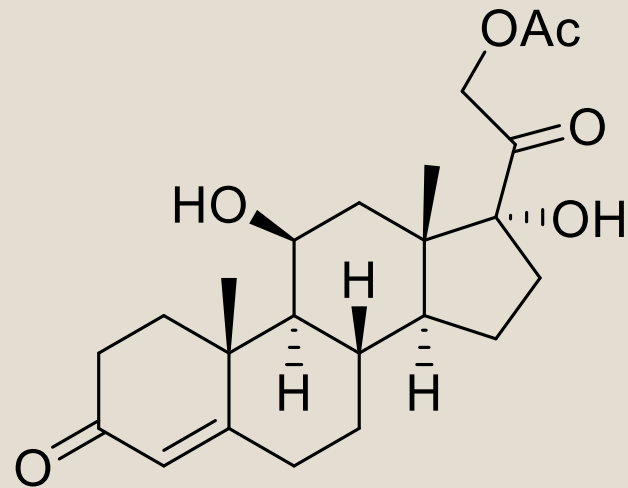
Process chemists role:

Identify the best way to synthesize that chemical

The Job of the Process Chemist

- **Find the chemical reactions**
 - Short synthesis
 - Keep it simple
 - Use inexpensive and safe materials
 - Make it pure
 - No pollution
- **Chemists don't do it on their own**
 - Chemical engineers
 - Analytical chemists
 - Microbiologists
 - Manufacturing staff

Hydrocortisone



Hydrocortisone Acetate (HA)

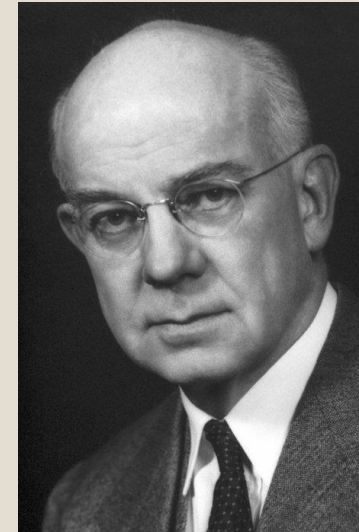
Miracle Drug of 1950



Philip S. Hench



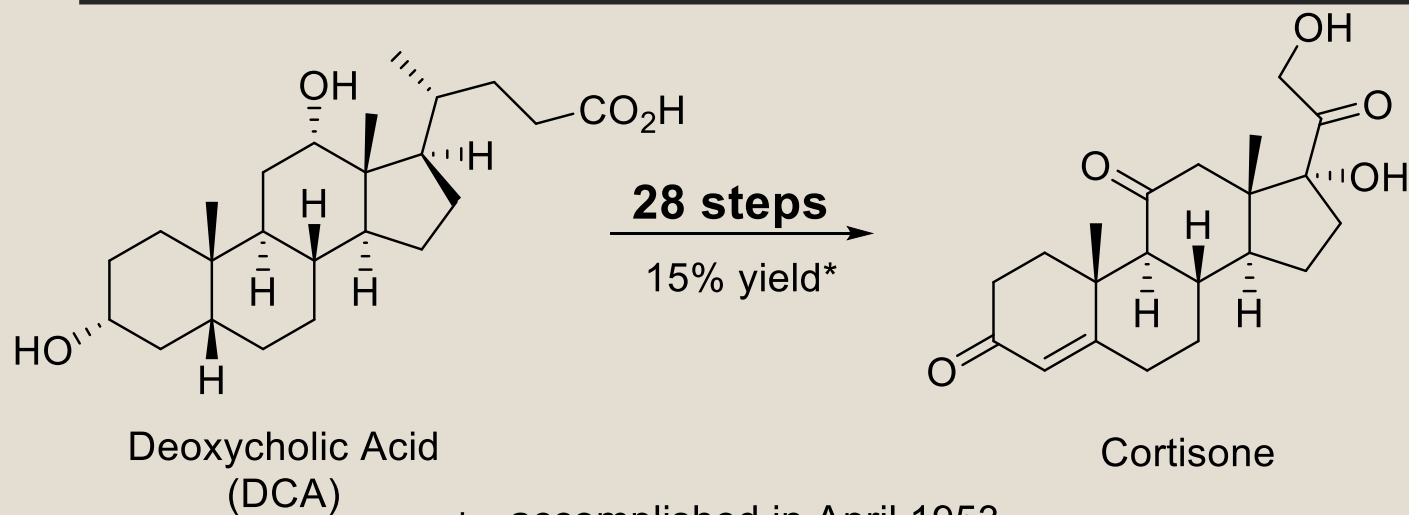
Tadeus Reichstein



Edward C. Kendall

..... was awarded jointly for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects

Hydrocortisone at Merck

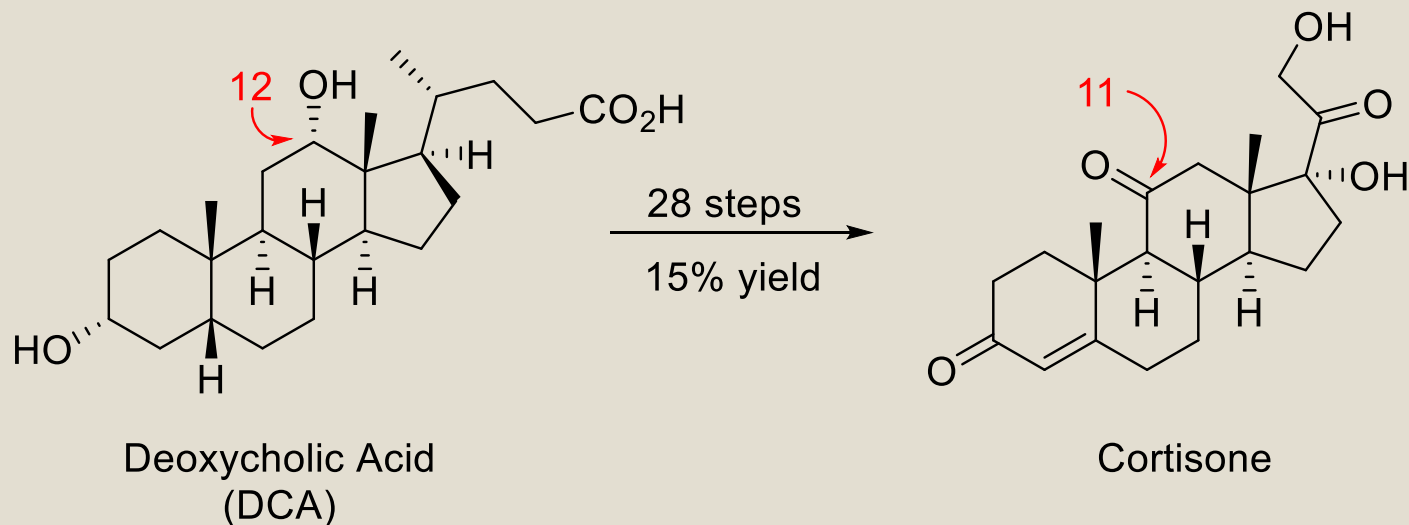


* - accomplished in April 1953

First commercial process from Merck

Ref: Seemon Pines, *Org. Proc. Res. Dev.*, **2004**, 8(5), pp 708-724

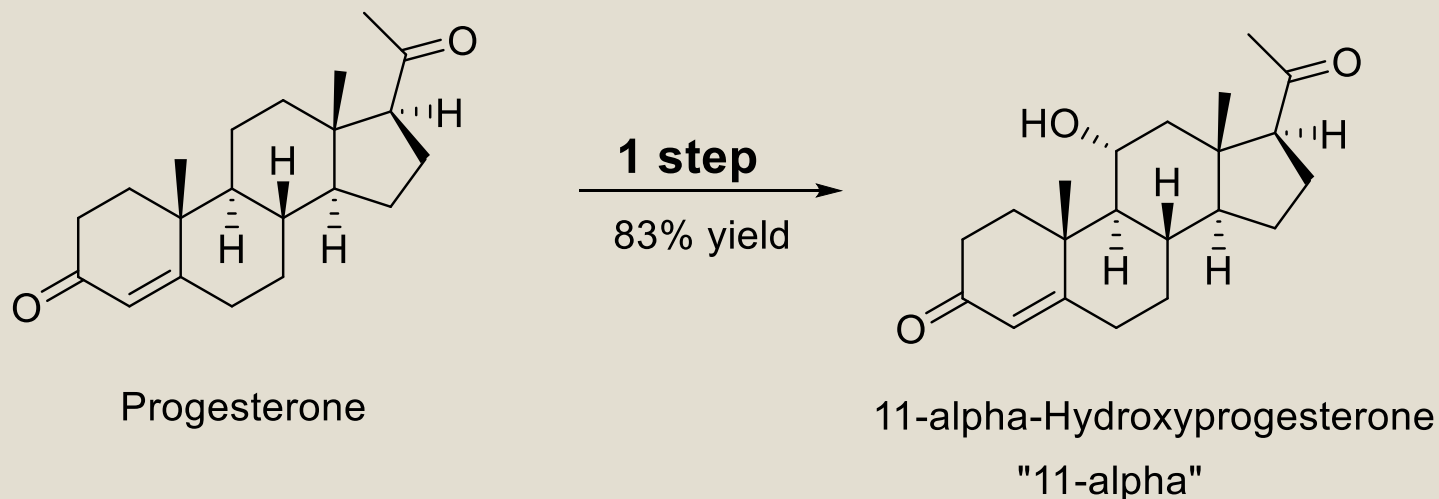
Hydrocortisone at Merck



The first eleven steps were simply to convert the 12-OH to the 11-ketone

Too many steps to be practical

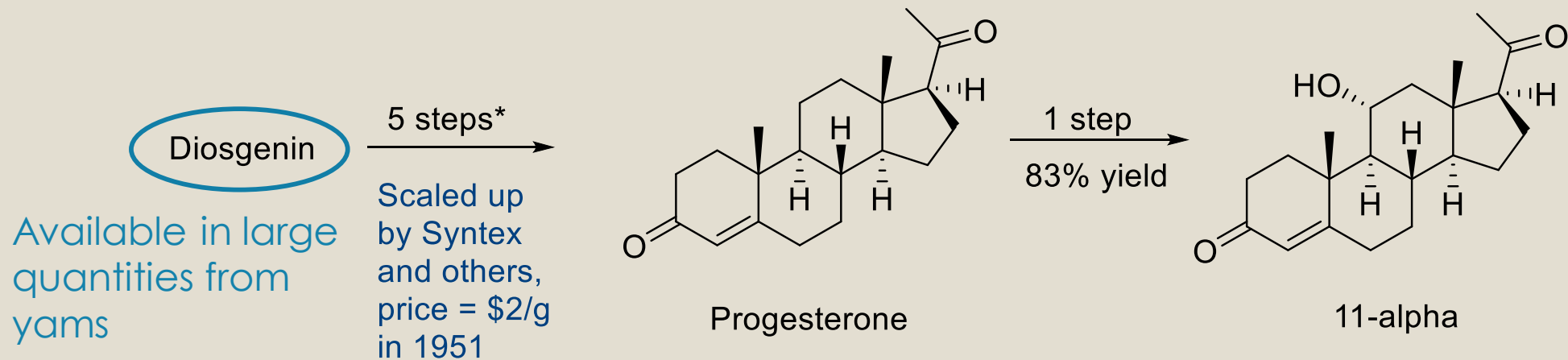
11-alpha-Hydroxyprogesterone



Peterson, Murray, Eppstein, Reineke, Weintraub, Meister and Leigh
J. Am. Chem. Soc., **1953**, 74, pp. 5933-5936
<Published December 5, 1952>

See also: John A. Hogg, *Steroids*, **1992**, pp. 593-616

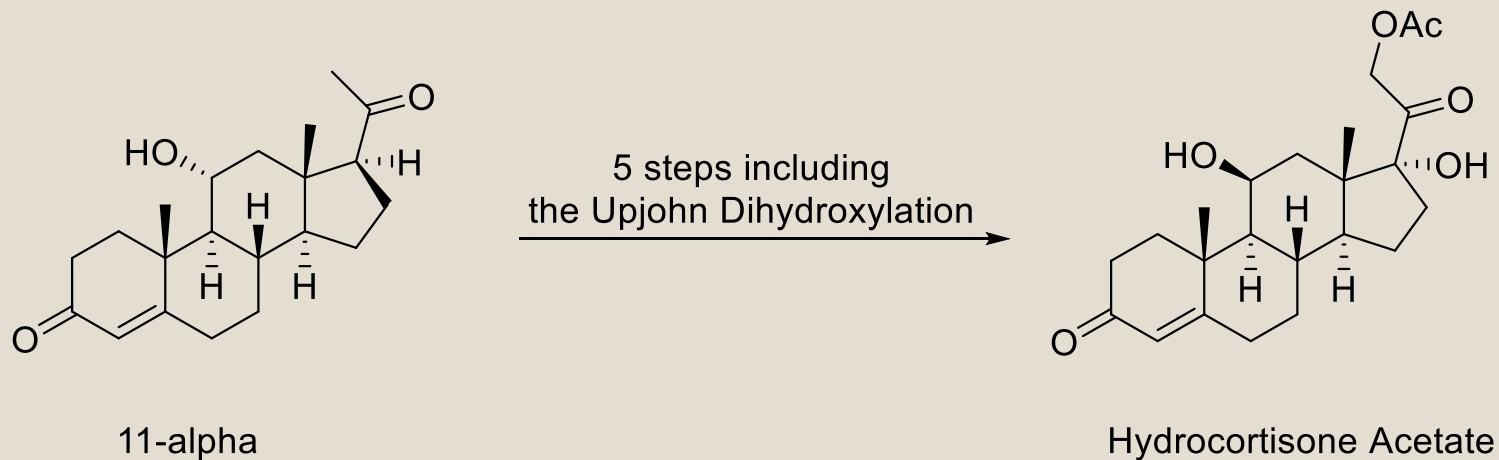
11-alpha-Hydroxyprogesterone



* - Marker degradation, first invented in 1940

Progesterone was a better starting material than Deoxycholic Acid

Side Chain Introduction

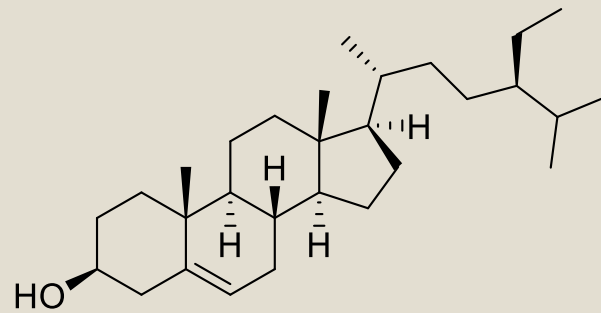


VanRheenen, Kelly and Cha, *Tetrahedron Letters*, **17**, pp. 1973-1976 (1976)

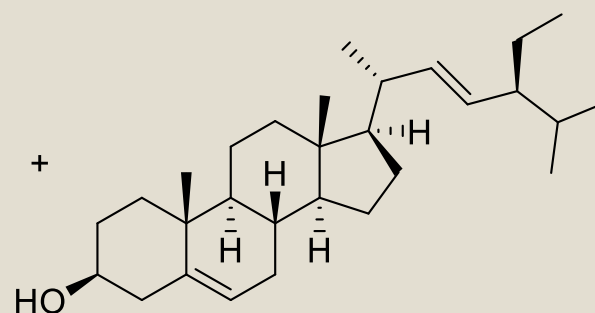
Progesterone

Soy bean processing by-products

Upjohn began work to separate in the 1940's



beta-Sitosterol
+
other sterols







Stigmasterol
(19%)

→ Progesterone

↓
Hydrocortisone

Corticosteroid Dominance by Upjohn



Betamethasone
Betamethasone Phosphate
Betamethasone Valerate
Cortisone Acetate
Dexamethasone
Dexamethasone Acetate
Dexamethasone Phosphate
Fludrocortisone Acetate
Fluorometholone
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Hemisuccinate
Prednisolone Anhydrous
Prednisolone Hydrous
Prednisolone Acetate
Prednisone
Prednisone Acetate
Triamcinolone
Triamcinolone Acetonide

Steroid Intermediates

Androstenedione (AD)
11 α Hydroxyprogesterone
17 α Hydroxyprogesterone
17 α Acetoxypregesterone
DBXI [17 α , 21-Dihydroxy-16 β -methyl-9 β ,
11 β -epoxy-pregna-1,4-diene-3,20-dione]
SD-V [17 α , 21-Dihydroxy-16 α -methyl-pregna-
4,9(11)-diene-3,20-dione,21-acetate]
SD-VI [17 α , 21-Dihydroxy-16 α -methyl-pregna-
1,4,9(11)-triene-3,20-dione]
SD-VII 17 α , 21-Dihydroxy-16 α -methyl-pregna-
1,4,9(11)-triene-3,20-dione,21-acetate]
T-1D [16 α , 17 α , 21-Trihydroxypregna-1,4,9
(11)-triene-3,20-dione,21-acetate]
3TR [21-Hydroxypregna-1,4,9(11)-16-tetraene-
3,20-dione-21-acetate]
1-2 Dihydrotriamcinolone [9 α Fluoro-11 β , 16 α ,
17,21-tetrahydroxypregna-4-ene-3,20-dione]

1987

Erythromycin
Erythromycin Stearate
Erythromycin Ethyl Succinate
Neomycin Sulfate
Novobiocin

Hormones





Ethisterone
Hydroxyprogesterone Caproate
Methyltestosterone
Progesterone
Testosterone
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate

Sterols

Sitosterol
Stigmasterol

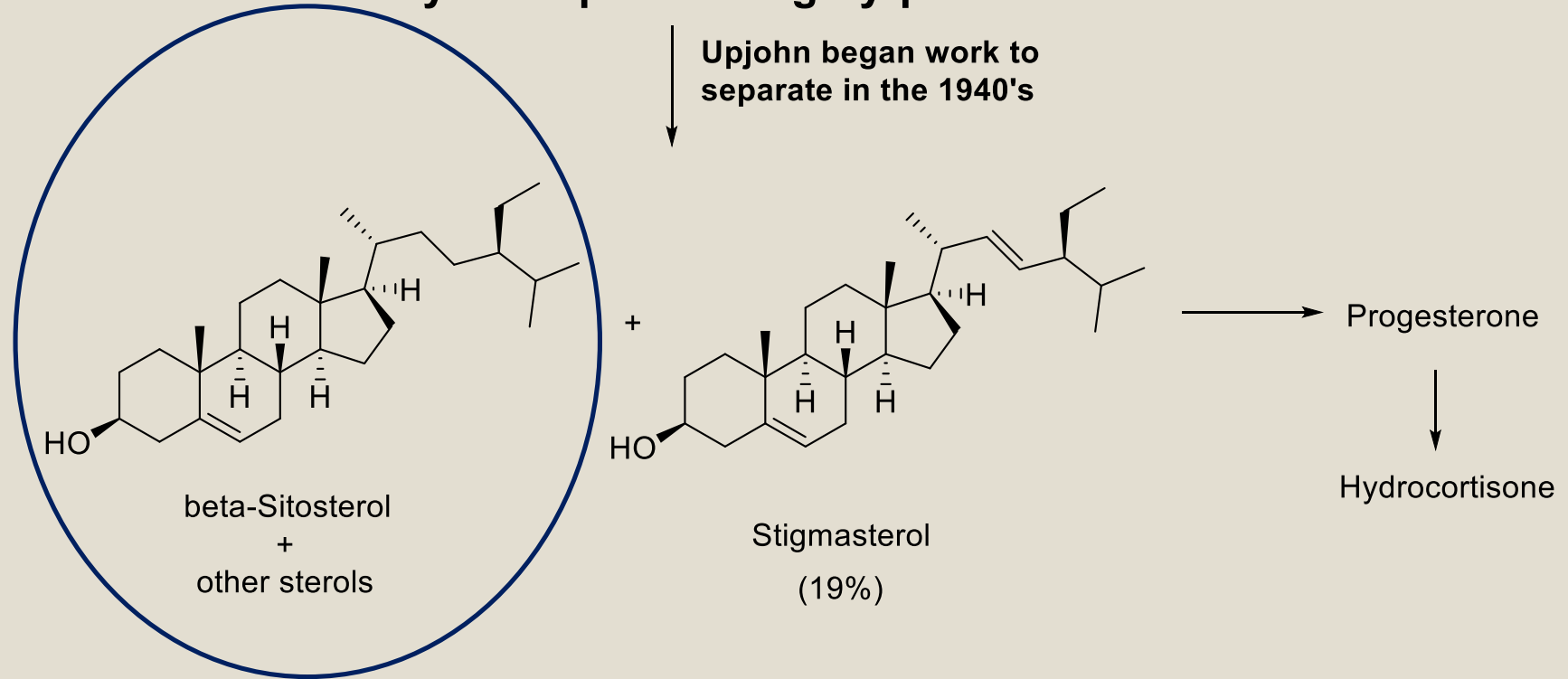
Specialty Chemicals

Cycloheximide
Streptozocin



Progesterone

Soy bean processing by-products

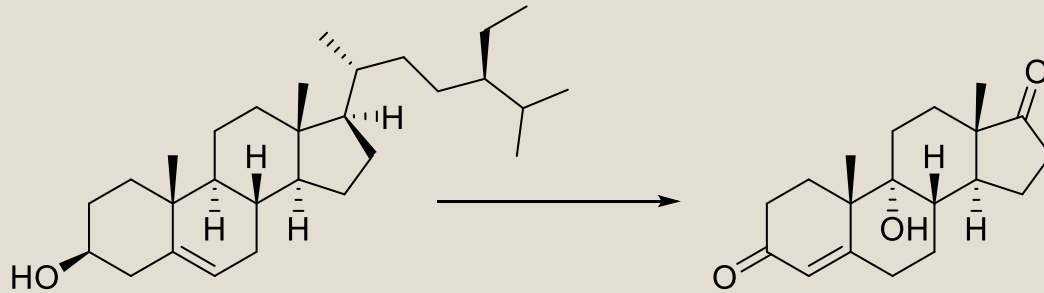


Every kg of stigmasterol led to 4+ kg of other sterols, leading to a large pile of sterols

Sterol “Pile”



Androstanes

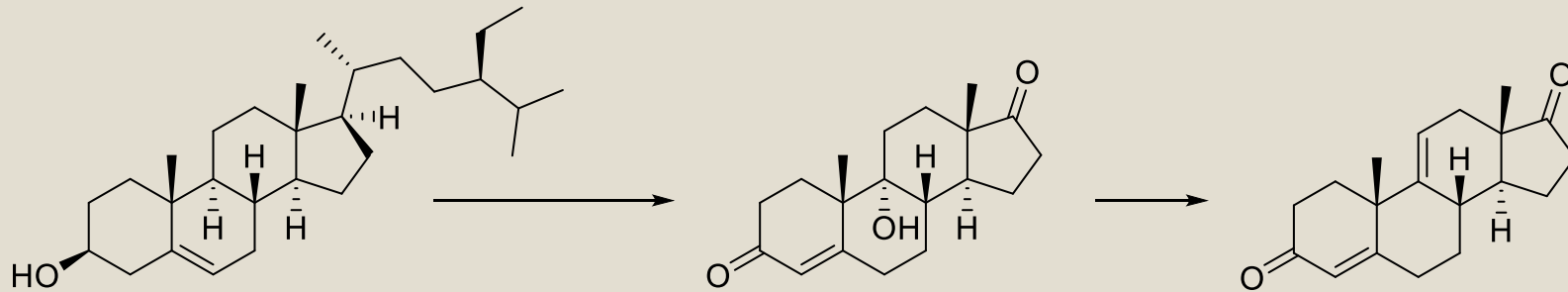


beta-Sitosterol
+
other sterols

9-Hydroxyandrost-4-ene-
3,17-dione, or "9-HAD"

Wovcha, Antosz, Knight, Kominek, and Pyke,
Biochim Biophys Acta, **531**, pp.308-320 (1978)

Androstanes



beta-Sitosterol
+
other sterols

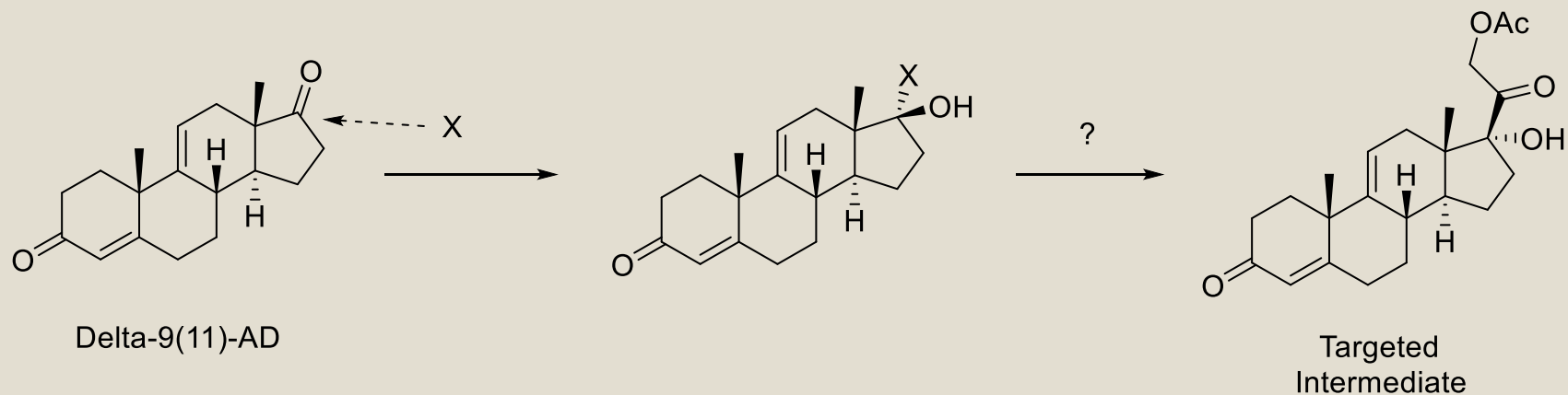
9-Hydroxyandrost-4-ene-
3,17-dione, or "9-HAD"

Delta-9(11)-AD

K.P. Shephard, **US 4,102,907**

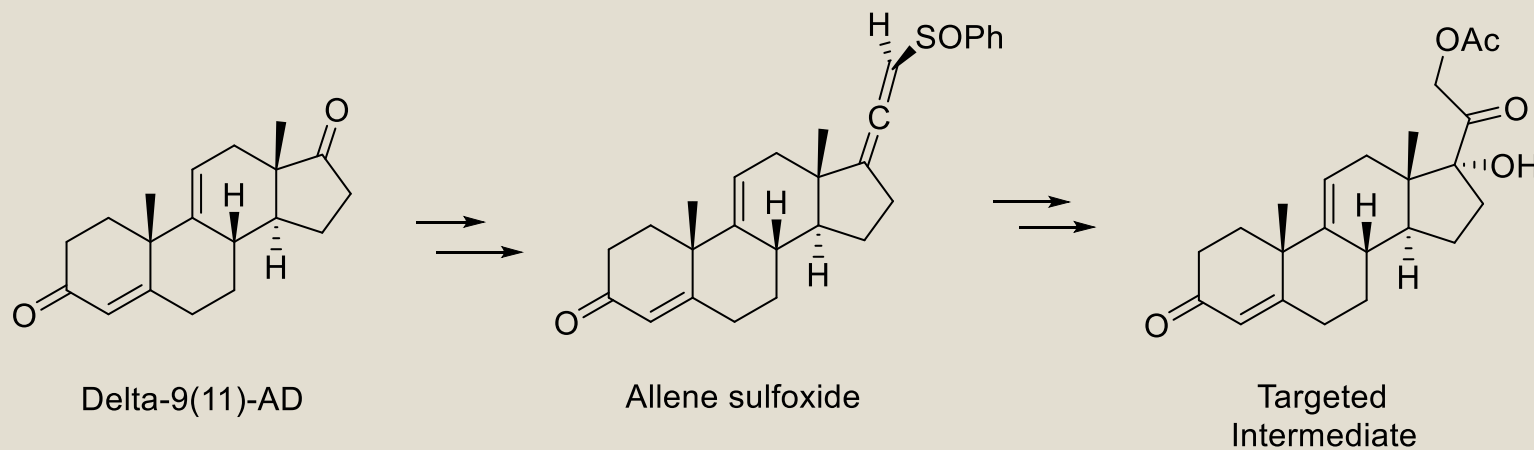
Can we find efficient processes for introducing side chains?

17-Ketone to Hydrocortis one



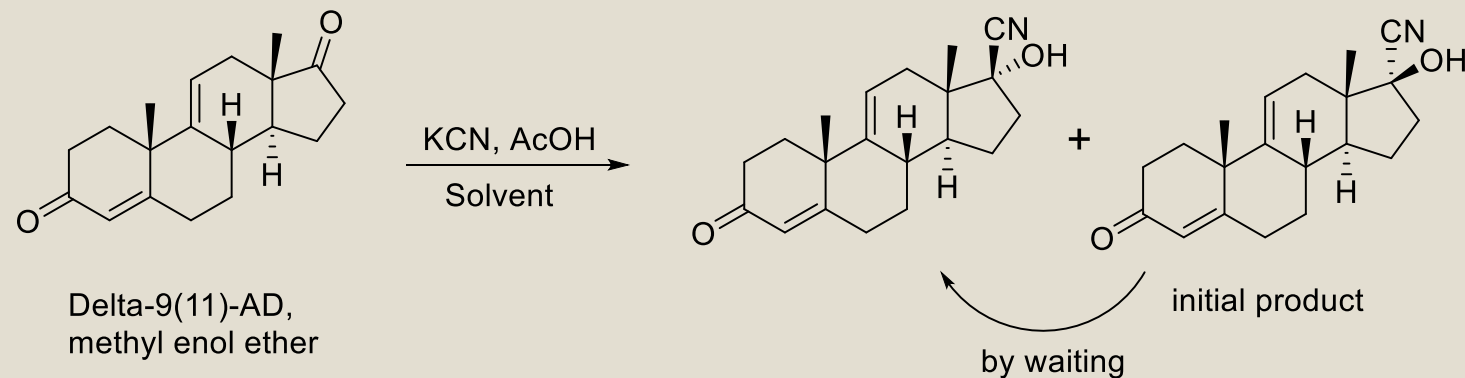
Attacking chemicals add from the wrong face so the “OH” ends up on the wrong side

Sneaky Solution



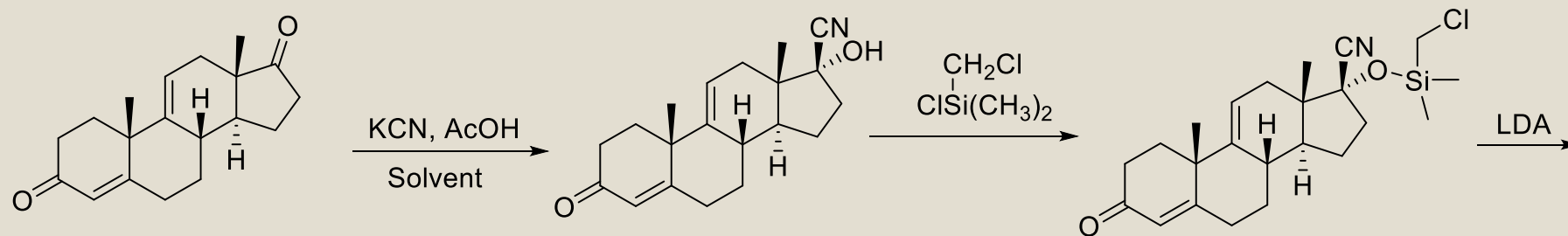
VanRheenen & Shephard, *J. Org. Chem.*, **1979**, 44, pp. 1582-1584

17-Ketone to Corticosteroids, Gen 2

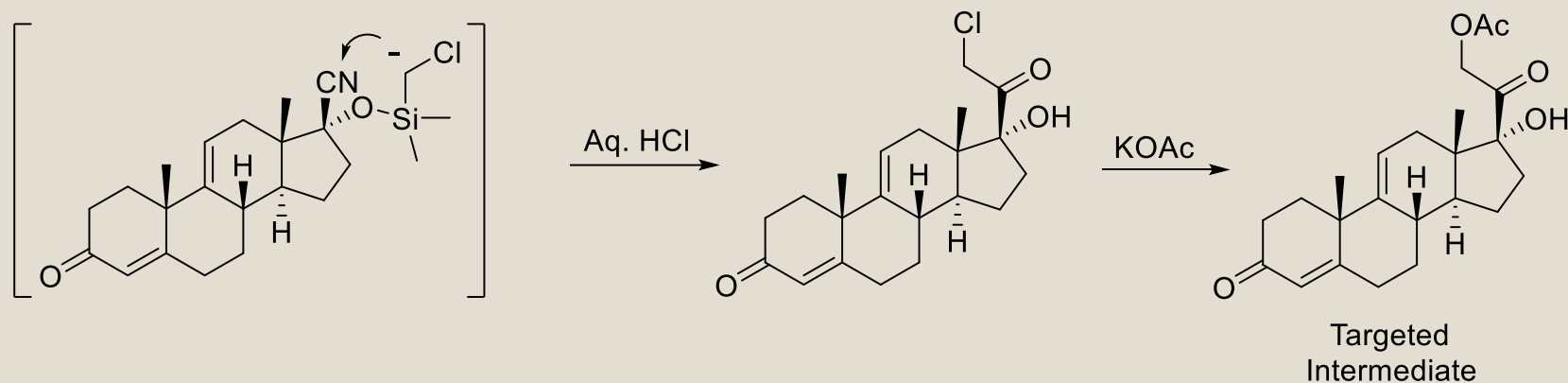


KCN is potassium cyanide, which was unique in its ability to attack from the other side

17-Ketone to Corticosteroids, SNAP

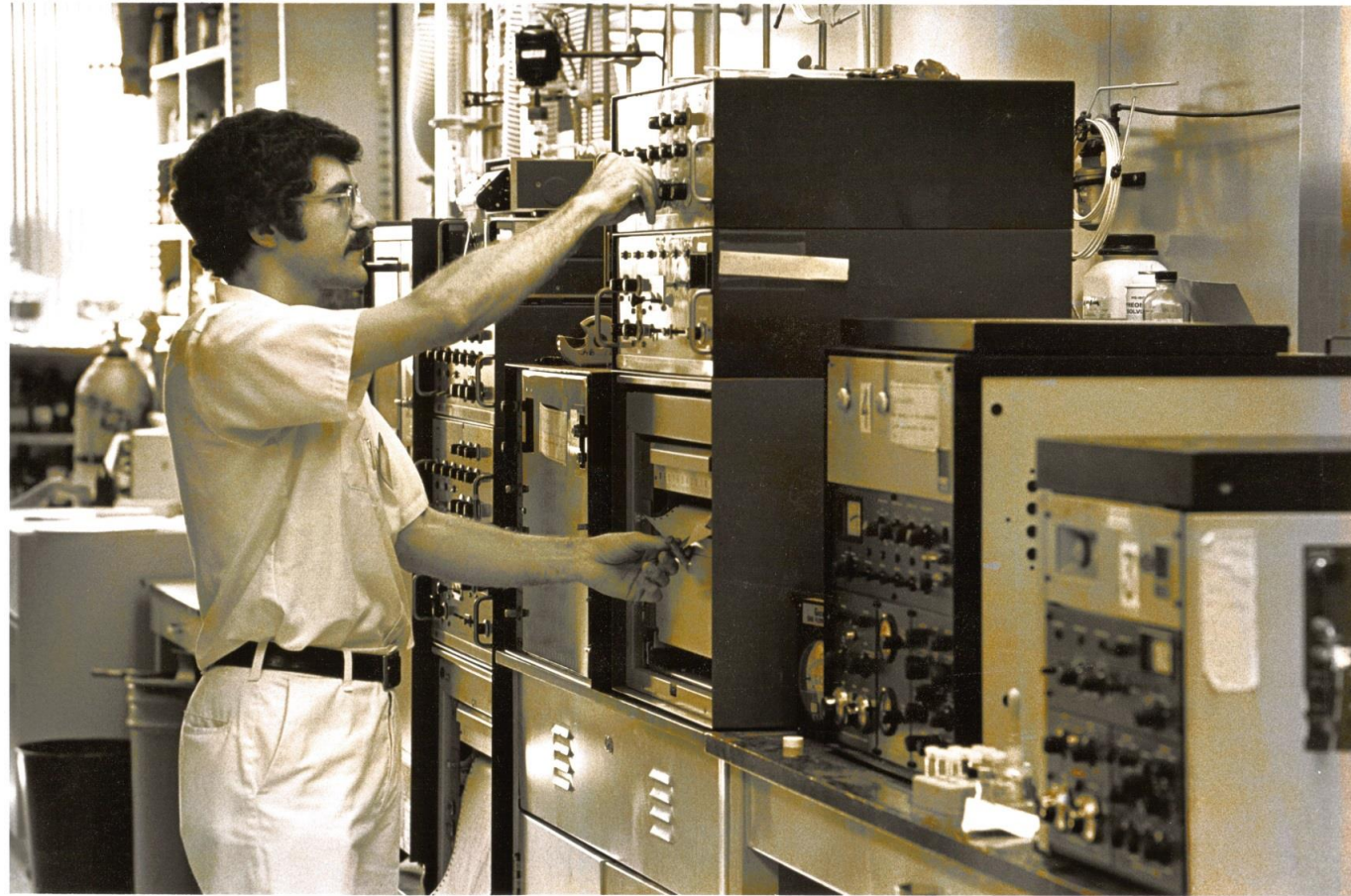


Delta-9(11)-AD,
methyl enol ether



Livingston, Pearlman and Denmark, **US**
4,977,255

Upjohn Labs



Final Comments About Upjohn

- Upjohn's success with steroids came from visionary leadership that encouraged creative bioconversions and chemical steps that dovetailed to give world-beating processes
- The rest of the world has simply tried to copy whatever Upjohn has done

Hydrocortisone Sculpture

